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Clinical and technical characteristics of intraoperative radiotherapy

Analysis of the ISIORT-Europe database

Intraoperative radiotherapy (IORT) refers to the delivery of radiation at the time of surgical intervention. IORT evolved as an attempt to improve the therapeutic ratio by achieving highly effective radiation doses while dose-limiting healthy structures are surgically displaced [38].

The first experience was documented by Comas and Prio in 1905 [6] for a case of endometrial cancer. Subsequently, other treatments using low energy x-ray setups were described in abdominal, thoracic and head and neck malignancies between the 1930s and 1950s [9]. The modern approach to IORT began with studies by Abe at the University of Kyoto in the early 1960s [1], who used single high doses of gamma rays from a cobalt unit and electrons from a betatron. In 1970, special IORT facilities with in-room conventional linear accelerators were established at the Howard University Hospital and the Massachusetts General Hospital. In the early 1990s, dedicated mobile electron linear accelerators and miniaturized low-energy x-ray machines were introduced into clinical practice worldwide.

In order to promote a scientific and professional approach to IORT activity, the International Society of Intraoperative Radiation Therapy (ISIORT) was founded in 1998 and the European sec-

Data from this work were presented at the ESTRO Anniversary Conference, London, UK, 8–12 May 2011 and at the ISIORT Meeting, Baveno, Italy, June 22–24, 2012.

Tab. 1 Radiation oncology centres that participated in data collection

Centre	Years	No. of cases	Percent
University Hospital Gregorio Marañon, Madrid, Spain	1995–2011	986	26.3
University Hospital, Salzburg, Austria	2006–2010	820	21.8
Hospital of Città di Castello, Italy	2005–2011	363	9.7
University Hospital, Verona, Italy	2006–2009	350	9.3
National Cancer Research Institute (IST), Genova, Italy	2009–2010	212	5.6
University Medical Center, Mannheim, Germany	2008–2010	179	4.8
Greater Poland Cancer Center, Poznan, Poland	2008–2010	155	4.1
University Hospital, Novara, Italy	2005–2011	149	4.0
Hospital S. Croce and Carle, Cuneo, Italy	2009–2010	85	2.3
Hospital San Giovanni Battista, Foligno, Italy	2009–2010	69	1.8
University Hospital Sant'Andrea, Roma, Italy	2009–2010	55	1.5
Hospital Santa Chiara, Trento, Italy	2010	51	1.4
Hospital San Francisco de Asís, Instituto Madrileño de Oncología, Madrid, Spain	1992–2002	50	1.3
San Filippo Neri Hospital, Roma, Italy	2009	37	1.0
Medical University of Lublin, Lublin, Poland	2009	34	1.0
Institute of the Mediterranean, Catania, Italy	2008–2011	33	1.0
Hospital, Treviso, Italy	2009–2010	32	1.0
Ramban Health Care Campus, Haifa, Israel	2006–2010	31	1.0
Hospital Santa Maria Nuova, Reggio Emilia, Italy	2006–2010	23	0.6
Regional Centre for the Fight against Cancer (CRLC) Val D'Aurelle, Montpellier, France	2008–2011	21	0.6
Hospital Multimedica, Castellanza, Italy	2008–2010	19	0.5

tion of ISIORT (ISIORT-Europe) was established in 2006. Among their other activities, ISIORT-Europe collected and recorded information regarding IORT activity at the affiliated centres in its database registry.

This article reports the data collected by the database registry of ISIORT-Europe with a focus on the clinical and technical aspects of IORT. Particular attention is given to the dominant tumour sites and the histological types identified.

Material and methods

From 2007, the ISIORT-Europe centres were invited to record information relating to IORT treatments in the database registry available at the ISIORT-Europe website. Real-time or retrospective data entry was allowed. Patient information was anonymized and integrated into a common database that included the following demographic, clinical and technical information: (a) patient age, gender and performance status according to the Karnofsky scale; (b) tumour data regarding site, histology, grading, staging according to TNM classification [30] and primary or recurrent tumour status before IORT; (c) treatment data including treatment intent, extension of surgery and treatment strategy; (d) specific IORT data regarding IORT treatment prior to/after tumour removal, number of fields, applicator diameter and bevel end angle, energy and type of radiation, total dose, use of bolus and reference isodose; (e) external beam radiation therapy (EBRT) data (when applicable) including cumulative dose and fractionation.

Results

The 21 centres from seven countries that participated in this survey recorded data from a total of 3754 IORT procedures performed between 1992 and 2011 (**Tab. 1**). The number of participating centres increased from three in 2007 (when the initiative was launched) to 21 in 2011. The average number of patients treated per year in each centre was 42, but exceeded 100 patients per year in three centres. Median patient age was 60.1 years with range of 5 months to 94 years. Gender was female in 77.9 and male in 22.1% of cases. Median performance status was 90% with a range of 40–100%. Tumour sites and histologies are listed in **Tab. 2**. Data from the five most frequently treated tumour types are specifically analysed and reported in detail.

Breast cancer

Data from 2395 women with breast cancer were collected (**Tab. 3**). In 2349 cases (98.1%), IORT was a component of radical treatment for primary, newly diagnosed disease and in 46 cases (1.9%) it was an attempt to rescue localized recurrent breast cancer. The patients enrolled in study protocols represented 33% of those treated by a single dose and 6.3% of those treated by a boost dose. IORT was used as single radiation treatment modality with doses of 18 Gy (8%), 20 Gy (23.8%) or 21 Gy (71.1%) and as a boost before or after EBRT with doses of 8–12 Gy. IORT was delivered before tumour removal in 39 and after tumour removal in 61% of cases. In instances of recurrent tumour, 99% of IORT treatments were given as an exclusive radiotherapy component without EBRT. IORT was performed either using electrons (in 92% of patients, treated in 20 centres) or a 50-kV x-ray source (the remaining 8% of patients, treated in a single centre). X-rays treatments were delivered by a spherical applicator inserted into the surgical cavity after tumour removal. The main technical characteristics of the electron treatments are described in **Fig. 1**.

Rectal cancer

Of the registered patients, 598 with rectal cancer were treated using IORT (**Tab. 3**). IORT was used for primary disease and isolated local recurrence in 514 (85.9%) and 84 (14.1%) cases, respectively. In 79% of cases, IORT was part of a multidisciplinary approach including EBRT, chemotherapy and surgery. In 91.9% of cases, the

surgeon obtained R0 resection. In 97% of cases, IORT was delivered after tumour removal. IORT was performed either by electrons (in 98% of cases, treated in 12 centres) or using a 50-kV x-ray source (in the remaining 2% of cases, treated in a single centre). X-ray treatments were delivered by a spherical applicator placed in the surgical bed after tumour removal. The technical characteristics of electron treatments are described in **Fig. 2**.

Sarcoma

Data from 221 cases of sarcoma were available (**Tab. 3**). IORT was used for primary tumour and local recurrence in 57.8 and 42.2% of cases, respectively. Radical excision was achieved in 86% of cases of primary tumour presentation. A multidisciplinary approach comprising EBRT, IORT, chemotherapy and surgery was performed in 16% of cases. IORT was delivered after surgical resection in 99% of cases. A single field was used in 74%, multiple fields in 15%, a field–in-field technique in 6% and adjacent fields were used in 5% of cases. IORT was performed either by electrons (in 90% of cases, treated in eight centres) or with a 50-kV x-ray source (in the remaining 10% of cases, treated in a single centre). X-ray treatments were delivered by a spherical applicator placed in the surgical bed after tumour removal. The technical characteristics of electron treatments are described in **Fig. 3**.

Prostate cancer

Of the reported patients, 108 with prostate cancer were treated with IORT (**Tab. 3**). All but three cases (97.2%) were primary, previously untreated tumours. IORT was used as a boost with doses of 8–15 Gy and as a single radiation modality with doses of 18–21 Gy. In 78% of cases, IORT was delivered prior to prostate removal. IORT was performed either by electrons (in 98% of cases, treated in five centres) or using a 50-kV x-ray source (in the remaining 2% of cases, treated in a single centre). X-ray treatments were delivered by a spherical applicator placed in the surgical bed after tumour removal. The technical characteristics of electron treatments are described in **Fig. 4**.

Pancreatic cancer

Data from 80 patients treated with IORT for pancreatic cancer were available (**Tab. 3**). Three cases (3.7%) were re-

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Clinical and technical characteristics of intraoperative radiotherapy. Analysis of the ISIORT-Europe database

Abstract

Background. A joint analysis of clinical data from centres within the European section of the International Society of Intraoperative Radiation Therapy (ISIORT-Europe) was undertaken in order to define the range of intraoperative radiotherapy (IORT) techniques and indications encompassed by its member institutions.

Materials and methods. In 2007, the ISIORT-Europe centres were invited to record demographic, clinical and technical data relating to their IORT procedures in a joint online database. Retrospective data entry was possible.

Results. The survey encompassed 21 centres and data from 3754 IORT procedures performed between 1992 and 2011. The average annual number of patients treated per institution was 42, with three centres treating more than 100 patients per year. The most frequent tumour was breast cancer with 2395 cases (63.8%), followed by rectal cancer (598 cases, 15.9%), sarcoma (221 cases, 5.9%), prostate cancer (108 cases, 2.9%) and pancreatic cancer (80 cases, 2.1%). Clinical details and IORT technical data from these five tumour types are reported.

Conclusion. This is the first report on a large cohort of patients treated with IORT in Europe. It gives a picture of patient selection methods and treatment modalities, with emphasis on the main tumour types that are typically treated by this technique and may benefit from it.

Keywords

Breast cancer · Rectal cancer · Sarcoma · Prostate cancer · Pancreatic cancer

Klinische und technische Charakteristika von intraoperativen Strahlentherapien. Analyse des Datenregisters der ISIORT-Europa

Zusammenfassung

Hintergrund. Die europäische Gruppe der Internationalen Gesellschaft für Intraoperative Radiotherapie (ISIORT-Europe) hat eine gemeinsame Analyse von technischen und klinischen Daten unternommen, um die Bandbreite der intraoperativen Techniken und Indikationen innerhalb ihrer Mitgliederinstitutionen zu erfassen.

Material und Methode. Im Jahr 2007 wurden die Mitgliederzentren eingeladen, demographische, klinische, dosimetrische und technische Details ihrer IORT-Verfahren in der gemeinsamen Registerdatenbank (http://www.isiort.org/htm/isiort_europe.htm) einzupflegen, wobei eine retrospektive Eingabe zulässig war.

Ergebnisse. An der Studie nahmen 21 Zentren teil, wobei pro Zentrum im Jahresdurchschnitt 42 Patienten behandelt wurden und 3 Institutionen über 100 Patienten pro Jahr therapierten. Insgesamt wurden im Zeitraum zwischen 1992 und 2011 Daten zu 3754 IORT-Verfahren erfasst. Die häufigste Tumorentität bildete das Mammakarzinom mit 2395 Fällen (63,8%), gefolgt von Rektumkarzinomen mit 598 Fällen (15,9%), 221 Sarkomen (5,9%), 108 Prostatakarzinomen (2,9%) sowie 80 Pankreaskarzinomen (2,1%). Zu diesen 5 Tumorarten werden klinische Angaben und technische Details der IORT berichtet.

Schlussfolgerung. Erstmals wurden anhand einer großen Patientenzahl Selektionen und Modalitäten zur intraoperativen Radiotherapie in Europa erfasst, mit dem Schwerpunkt auf die hauptsächlich mittels IORT behandelten Tumorentitäten, die von dieser Therapie profitieren könnten.

Schlüsselbegriffe

Brustkrebs · Rektumkarzinom · Sarkom · Prostatakarzinom · Pankreaskarzinom

Tab. 2 Tumour sites treated with intraoperative radiation therapy

Tumour site	No. of cases	Percent
Breast	2395	63.8
Rectum	598	15.9
Soft tissue sarcoma	221	5.9
Prostate	108	2.9
Pancreas	80	2.1
Oesophagus	51	1.4
Uterine cervix	46	1.2
Stomach	44	1.2
Brain	34	1.0
Head and neck	23	0.6
Ovary	16	0.5
Kidney	8	0.2
Biliary tract	7	0.2
Colon	6	0.2
Lung	6	0.2
Sacrum	6	0.2
Bladder	5	0.1
Adrenal glands	5	0.1
Uterine body	4	0.1
Vertebral body	2	0.1
Other or undefined sites	89	2.0

Tab. 3 Main patient and treatment characteristics in relation to the tumour site

	Breast (N=2395)	Rectum (N=598)	Soft tissue/bone (N=221)	Prostate (N=108)	Pancreas (N=80)
Centres	100%	57.1%	38.1%	23.8%	38.1%
Median age Range	60.8 years 16–89 years	63.0 years 26–94 years	43.8 years 2–88 years	67.2 years 51–83 years	64.6 years 34–78 years
Gender	M: 0% F: 100%	M: 63.9%, F: 36.1%	M: 51% F: 49%	M: 100% F: 0%	M: 57.5% F: 42.5%
Histology	DC: 96.3% LC: 3.7%	ACA: 98.7% Other: 1.3%	Liposarcoma: 23.5% Fibrohistiocytoma: 8.1% Leiomyosarcoma: 7.7% Ewing sarcoma: 7.2% Synovial sarcoma: 7.2% Rhabdomyosarcoma: 4.1% Unspecified: 42.2%	ACA: 100%	ACA: 100% (with neuroendocrine component in 6.2%)
Stage	Tis: 1.6% T1: 82.5% T2: 15.7%	T1: 3.7% T2: 11.1% T3: 70.2% T4: 15.0%	T1: 13.0% T2: 57.0% T3: 17.0% T4: 13.0%	T2a: 12.0% T2b: 7.8% T2c: 26.0% T3a: 42.8% T3b: 7.8% T4: 3.9%	T1: 6.5% T2: 35.5% T3: 25.8% T4: 19.4%
Single-shot Boost	51.9% 48.1%	16.2% 83.8%	51.6% 48.4%	52.3% 47.7%	60.0% 40.0%
Curative Palliative	100% 0%	95.0% 5.0%	90.0% 10.0%	100% 0%	81.2% 18.8%
Prospective study	All: 19.4% Single-shot: 33.0% Boost: 6.3%	0%	0%	80.6%	0%

M males, *F* females, *DC* ductal carcinoma, *LC* lobular carcinoma, *ACA* adenocarcinoma.

current tumours. IORT was given to non-resectable tumour and following pancreatectomy in 25 and 75% of cases, respectively. The technical characteristics of electron treatments are described in **Fig. 5**.

Discussion

The survey collected data from 21 institutions, which represented 39% of the IORT centres active in Europe in 2009 [9]. The number of collaborating centres increased from three in 2007 to 21 in 2011, demonstrating increased interest in this initiative.

Breast cancer

During the past decades, clinical indications for IORT treatment have evolved significantly and expert centres have incorporated this technique into breast cancer therapy. Our database shows that IORT was used to treat breast cancer at all centres, whereas only a few institutions treated other tumour types (**Tab. 3**). This fact may be related to the proportionately higher incidence of breast cancer compared to other tumours amenable to IORT and to the launch of large clinical trials exploring IORT as a single radiation modality. Such trails aim to shorten overall treatment times in loco-regional therapy, improve patients' quality of life and reduce the waiting lists in radiotherapy centres [35, 37]. The efficacy of single-shot IORT—which represents a partial breast irradiation (PBI) strategy—has been under investigation during the last few years, particularly for selected groups of patients [20, 31, 32]. In this regard, the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) formulated quite similar general criteria for the recommendation of PBI [22, 29]. However, only 33% of patients treated by a single radiation fraction were included in study protocols, meaning that a large total number of patients were treated and implying that high-dose IORT is considered current clinical practice on the basis of preliminary results of clinical trials [26]. The dose level most frequently adopted in our survey was 21 Gy, as in the intraoperative radiotherapy with electrons (ELIOT) trial [20].

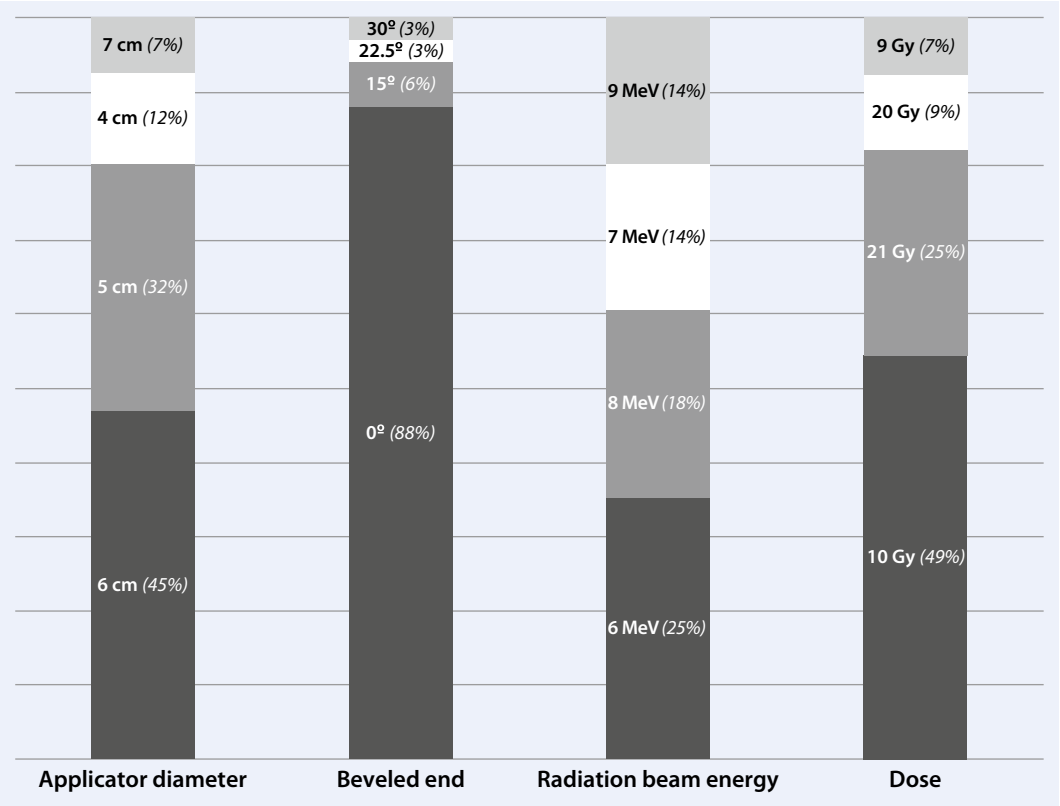

Fig. 1 ◀ Main technical characteristics of intraoperative radiotherapy by electrons for breast cancer. In 192 additional treatments (8%), a 50-kV x-ray source was used with a spherical applicator placed in the surgical bed after tumour removal

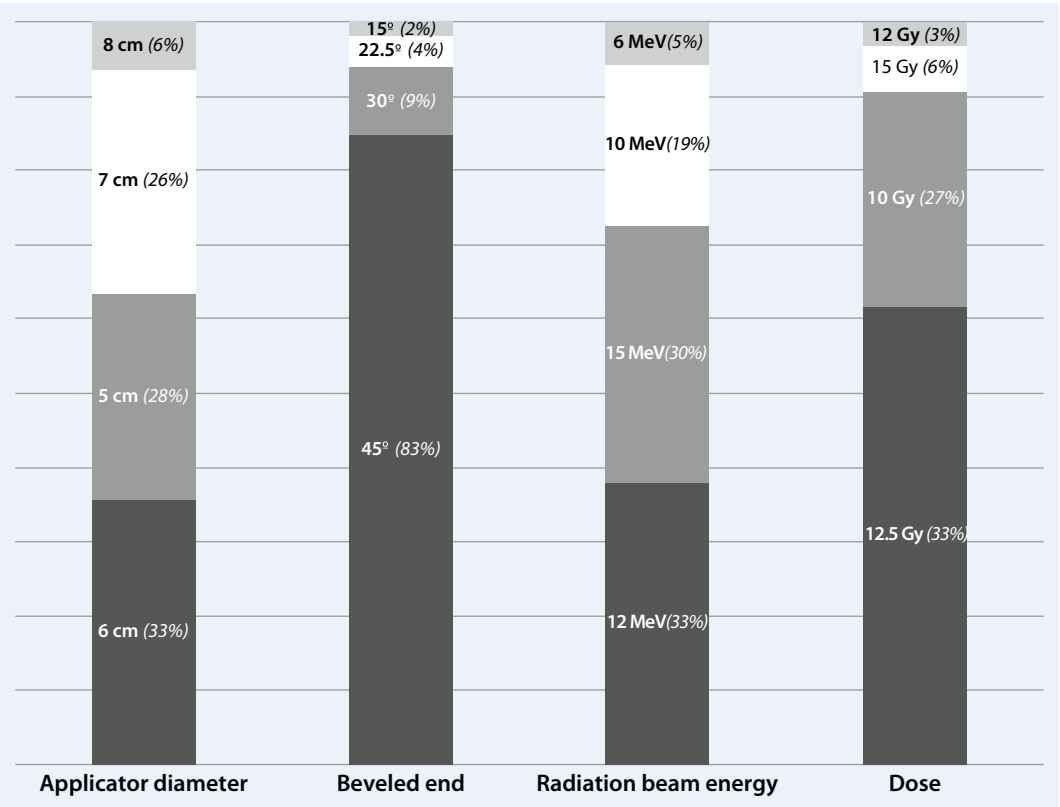

Fig. 2 ◀ Main technical characteristics of intraoperative radiotherapy by electrons for rectal cancer. In 13 additional treatments (2%), a 50-kV x-ray source was used with a spherical applicator placed in the surgical bed after tumour removal

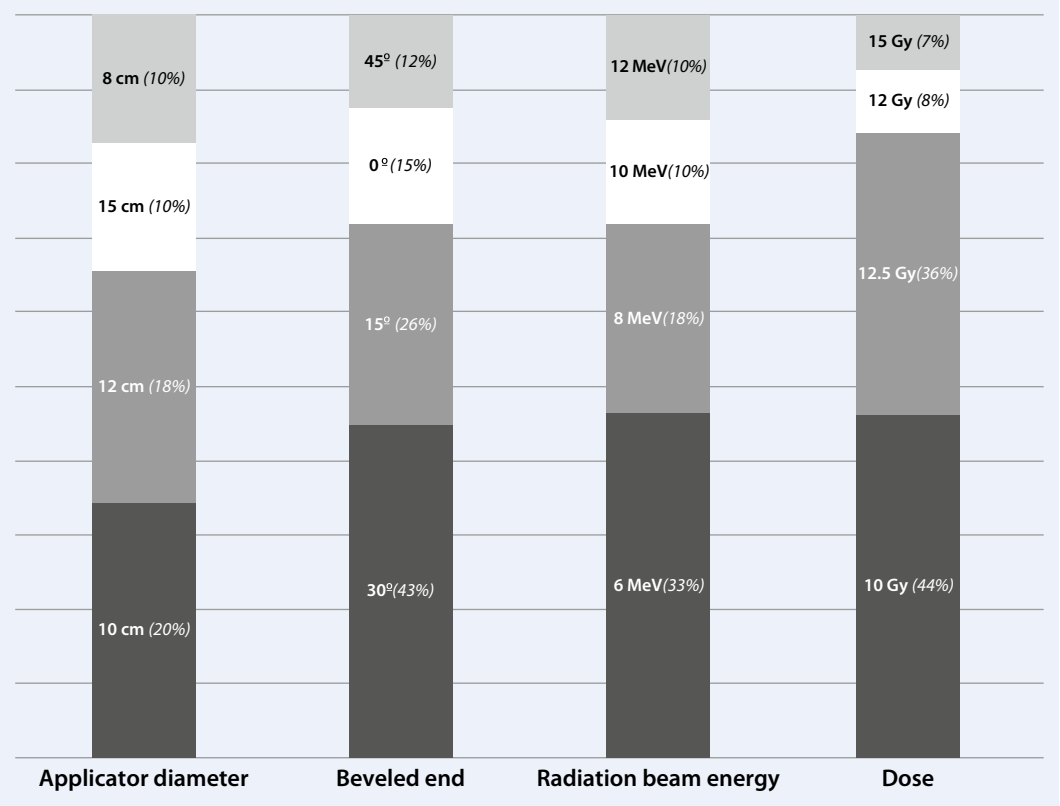

Fig. 3 ◀ Main technical characteristics of intraoperative radiotherapy by electrons for sarcoma. In 22 additional treatments (10%), a 50-kV x-ray source was used with a spherical applicator placed in the surgical bed after tumour removal

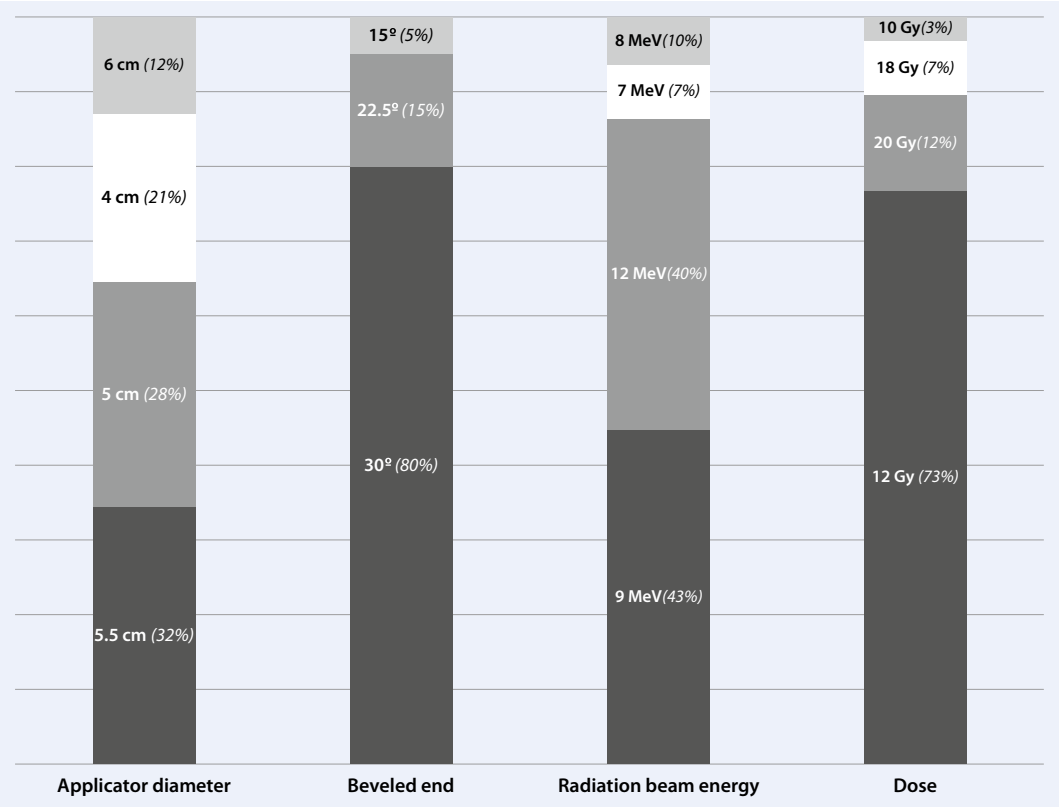

Fig. 4 ◀ Main technical characteristics of intraoperative radiotherapy by electrons for prostate cancer. Two additional treatments (2%) were given using a 5-kV x-ray source with a spherical applicator placed in the surgical bed after tumour removal

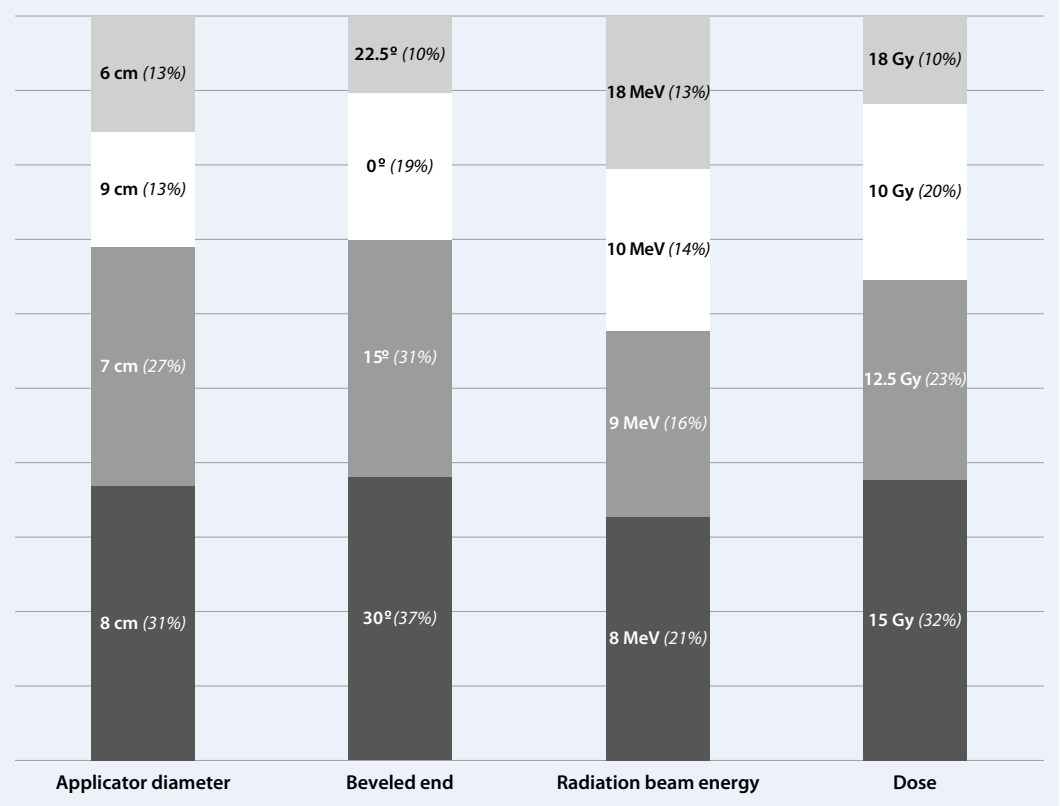

Fig. 5 ◀ Main technical characteristics of intraoperative radiotherapy by electrons for pancreatic cancer

A single fraction was also used to treat the surgical bed after local tumour recurrence in a relevant number of patients, i.e. 330 cases, representing 13.8% of all breast IORT procedures in our survey.

IORT as a boost technique was used in about half of the patients (48%) outside of clinical trials, meaning that the approach of anticipated boost has been adopted as current practice. In expert IORT institutions, dose intensification has been shown to achieve outstandingly low rates of local recurrence in previously reported clinical studies [27]. The relatively low percentage (8%) of x-ray treatments may be due to the fact that in comparison to centres using electrons, only a small fraction of the existing x-ray centres contributed to the registry.

Rectal cancer

IORT in rectal cancer aims to improve local control in locally advanced high-risk disease and in recurrent tumours where pelvic relapse is responsible for therapeutic failure. Up to 50% of cases lead to metastatic evolution and consequently ominous prognoses. Most cases in our analysis presented with a locally advanced stage and a non-negligible percentage of patients (14%) were treated for locally recurrent disease. In the majority of cases, IORT was given with curative intent as a boost intensification dose and was part of a multidisciplinary approach including surgery, EBRT and chemotherapy.

Numerous studies in the literature show a favourable local effect of IORT, with high rates of local control in advanced primary and recurrent tumours [5, 10, 14, 18, 36]. However, the only randomized trial comparing conventional preoperative external radiotherapy with the same treatment plus IORT failed to show an advantage of the experimental arm [8]. The European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer in 605 patients showed a local recurrence rate of only 12% in a very high-risk group of patients [17]. For this group, the addition of hyperthermic intraperitoneal chemotherapy to IORT treatment and cytoreductive surgery was recently encouraged [12]. A collective effort in the design and enrolment of patients in prospective clinical trials may generate evidence useful for tailoring the indications for IORT to rectal cancer [34]. The technical parameters of our survey were adequate to treat the presacral space and were similar to those reported in the European pooled analysis [17].

Sarcoma

IORT is used in the multimodality treatment of sarcoma because it enables the application of high-dose radiation to the target volume using a lower EBRT dose, which results in correspondingly reduced doses to surrounding healthy tissues. Data in the literature show that IORT is able to achieve high control rates in selected cases of soft tissue sarcoma localized to the trunk or extremities [4, 13, 19, 21, 28].

Histologically, our analysis showed quite heterogeneous subtypes, as in many other sarcoma series. Almost half of the patients had recurrent tumours, which are a challenge in rescue treatments. IORT was also given as a boost in combination with EBRT to obtain dose intensification. In terms of the technical aspects, soft tissue sarcoma required a wide range of applicator diameters and

bevel angles, reflecting the frequently large tumour extension and the postresection tumour bed in soft tissues. Moreover, many cases required complex irradiations with multiple fields or field-in-field techniques with high-energy electrons (up to 18 MeV) and doses of up to 25 Gy. Similar treatment modalities were described in other reports [4, 13, 19, 21].

Prostate cancer

The rationale for IORT dose escalation for prostate cancer is based on the demonstration of a dose–response relationship and the low α/β value in the linear quadratic model [16]. Likewise, the exploitation of this principle is being increasingly investigated in EBRT [3, 8]. Early data on IORT in locally advanced prostate cancer come from Kyoto University and the Saitama Cancer Centre in Japan, where the authors treated patients without prostatectomy [2, 11]. More recent experiences were reported by Italian authors using IORT in combination with radical prostatectomy and regional lymph node dissection before or after the surgical procedure [15, 23, 25]. A relevant percentage (81%) of patients were included in prospective institutional study protocols. In most cases, IORT was used as a boost dose prior to prostate removal. In the case of single-shot radiation, a dose of 18–21 Gy was adopted, similar to the breast cancer model. The diameter and bevel end angle of the applicators were selected on the basis of target dimensions, considering a margin of at least 5 mm around the prostate and the necessity to reach the target underneath the pubic arch to spare the bladder. The electron beam energy—between 9 and 12 MeV—depended on the depth of the target and the position of the rectum, which should be spared. Dose levels were in the range of those of a recently published series [16].

Pancreatric cancer

IORT could be an interesting approach for dose intensification to improve local control in the therapy of locally advanced pancreatic cancer. This remains one of the most lethal types of malignancy, with an overall 5-year survival rate of less than 5%. Several literature studies have described favourable effects of IORT in pancreatic cancer, but the results preclude clear interpretation since this technique was used in the context of multiple treatment strategies [24, 33].

The registry collected data from patients with locally advanced stages (mainly T2–T4), treated in most cases with curative intent after tumour resection. Case selection criteria corresponded quite well to those of other literature studies [33]. From the technical point of view, quite large applicator diameters were used with a large range of beam energies and dose levels. This most likely results from the need to irradiate the pancreas or the tumour bed and the regional lymph nodes.

Conclusion

This the first report of data from a large collection of clinical experience in patients treated with an IORT component in Europe. It gives an overview of practice-oriented patient selection, describes treatment modalities and analyses methodology and treatment-related decisions for a number of tumour types that are currently treated by this technique and may benefit from it. The main limitations of the present survey are the number of participating institutions—which represent less than half of the clinically active centres in Europe—and the unavailability of data concerning intraoperative brachytherapy and treatment outcomes. Further data analyses could enhance multi-institutional performance and serve as a basis for designing clinical trials in an effort to define the role of IORT in tailored multimodality therapeutic approaches.

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